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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,714	02/28/2002	Daphna Havkin-Frenkel	DMCI-0099	7483

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EXAMINER	
COLLINS, CYNTHIA E	
ART UNIT	**PAPER NUMBER**
1638	

DATE MAILED: 12/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,714	HAVKIN-FRENKEL ET AL.	
	Examiner	Art Unit	
	Cynthia Collins	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16 and 19-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16 and 19-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed September 10, 2004 has been entered.

Claims 1-15, 17-18 and 26-29 are cancelled.

Claims 16 and 19 are currently amended.

Claims 30-31 are withdrawn.

Claims 16 and 19-25 are pending and are examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All previous objections and rejections not set forth below have been withdrawn.

Claim Rejections - 35 USC § 112

Claims 16 and 19-25 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons of record set forth in the office action mailed May 6, 2004.

Applicants' arguments filed September 10, 2004 have been fully considered but they are not persuasive.

With respect to the enablement of functional variants, Applicants respectfully note that the claims as amended do not recite any functional variants as discussed above under written description. To the extent the rejection is based on functional variants, reconsideration is respectfully requested. (reply page 5)

The Examiner acknowledges that that the claims as amended do not recite any functional variants, but the rejection is maintained for the reasons set forth below.

Applicants maintain that the skilled artisan clearly understands that the techniques of genetic engineering and manipulation are not sequence specific and can be broadly applied to any sequence, including the novel sequences disclosed herein. Applicants respectfully assert that the sequences provided can be used in a variety of genetic engineering methods and that Applicants need not teach what is well-known (the methods) which can be applied with the sequences to produce a plant or plant cells expressing the sequence. Applicants also assert that given the sequences provided in the specification, the skilled artisan can apply any of the well-established techniques for genetic engineering and can powerfully select for the desired transgenic plant or cell. Applicants maintain that this would not require inventive effort or undue experimentation but rather would be only routine. Applicants further assert that since the specification must only enable one to make and use the invention and need not eliminate routine efforts on the part of the skilled artisan, the requirements 35 U.S.C. 112, first paragraph are satisfied. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. 112, first paragraph with respect to the use of genetic engineering methods for introducing the nucleic acid of SEQ ID NO:1, or expressing the protein of SEQ ID NO:2. (reply pages 5-6)

The Examiner maintains that outstanding rejection was not predicated on the failure to provide sufficient guidance with respect to the use of genetic engineering methods for introducing nucleic acids into plants, i.e. plant transformation methods. The outstanding rejection

was predicated in part on the failure to provide sufficient guidance with respect to the use of genetic engineering methods other than transformation with a nucleic acid encoding the p-hydroxybenzaldehyde synthase of SEQ ID NO:2 for the purpose of genetically engineering *Vanilla planifolia* to overproduce enzymes associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde (pages 8-9 of the office action mailed May 6, 2004).

In this regard the Examiner notes that the rejected claims are not limited to transforming a plant with a nucleic acid of SEQ ID NO:1 or a nucleic acid encoding a polypeptide of SEQ ID NO:2. The rejected claims only require "genetically engineering the *Vanilla planifolia* to overproduce one or more enzymes associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde having the amino acid sequence of SEQ ID NO:2". Such claims read on the use of any type of genetic engineering technology that may or may not require the use of plant transformation and that may or may not require the use a nucleic acid of SEQ ID NO:1 or a nucleic acid encoding a polypeptide of SEQ ID NO:2. For example, such a plant could be produced by mutation breeding, or by transformation of a plant with a transcription factor coding sequence. All that is required is the production of a plant that overproduces one or more enzymes associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde having the amino acid sequence of SEQ ID NO:2.

Given that the rejected claims are not limited to transforming a plant with a nucleic acid of SEQ ID NO:1 or a nucleic acid encoding a polypeptide of SEQ ID NO:2 and encompass the use of any and all methods of genetically engineering *Vanilla planifolia* to overproduce one or more enzymes associated with a chain shortening of p-coumaric acid to p-hydroxybenzaldehyde having the amino acid sequence of SEQ ID NO:2, and given the lack of guidance in the

disclosure and in the prior art for genetically engineering *Vanilla planifolia* to overproduce such enzymes other than by transformation of *Vanilla planifolia* with a nucleic acid encoding the p-hydroxybenzaldehyde synthase of SEQ ID NO:2, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

Applicants respectfully note in particular that the portions of the specification cited by the Examiner from pages 15 and 16 pertaining to the involvement of multiple enzymes in the metabolism of vanilla in cultured *V. planifolia* relate to improving vanillin production in tissue culture by manipulation of culture conditions and do not necessarily equate to manipulation of enzymes of the vanillin biosynthetic pathway. Applicants also note that the text on page 20 states that with respect to the conversion of 4-coumaric acid to 4-hydroxybenzaldehyde, "this reaction may play a more important rate-controlling function in intact vanilla beans." Applicants further note that the disclosure at page 32, lines 13-17 indicates that "it is clear that at least one chain shortening enzyme is involved in the conversion from CA to BA, and that this step does not appear to be rate-limiting in cultured cells. However, some evidence indicates that it is the rate-limiting step in intact vanilla beans." (reply pages 6-7)

Applicants further maintain that the Examiner's whole line of reasoning is apparently predicated on the idea that only overproducing a, or the, rate-limiting step enzyme can be helpful in improving production of the end-product of a biosynthetic pathway. In this regard Applicants respectfully assert that the skilled artisan could readily appreciate that improving vanillin production could result, for example, by driving a greater percentage of the p-coumaric acid to p-hydroxybenzaldehyde, which in turn could drive the next reaction step to the HBA side of the

scheme, and further downstream to vanillin. Furthermore, Applicants maintain that the overproduction of the chain shortening enzyme could readily be envisioned to, for example, offset the affect of VAD as indicated on page 55, which can impact the amount of 4-hydroxybenzaldehyde, by dehydrogenation. Overproduction of the enzyme which produces 4-hydroxybenzaldehyde (from 4-coumaric acid) would help maintain concentrations and keep the main pathway supplied, thereby improving vanillin production. Applicants additionally point out that the data from kinetic experiments (see e.g. Example 12, page 68, lines 18-27) suggest that positive cooperativity is feature of the chain shortening enzyme, and that such a feature is consistent with a multimer, and increasing the production of subunits is likely to enable the multimeric and positively cooperative units to form and function. (reply page 7)

Applicants additionally maintain that other disclosure also enables the skilled artisan to make and use the invention for improving vanillin production with an expectation of success. For example, on page 69 it is stated that "non-oxidative chain shortening appears to be the major route to vanillin precursors in *V. planifolia* cell cultures." Thus, the skilled artisan would appreciate that by increasing production of the chain-shortening enzyme, the vanillin precursors could be increased, thus improving the production of vanillin. Again at worse case, no undue experimentation is required. The skilled artisan could resort to routine measurement of vanillin by art-known methods to determine whether the genetic engineering of the *V. planifolia* had been successful in improving vanillin production. (reply pages 7-8)

The Examiner maintains the line of reasoning set forth in the previous office action at pages 6-8 citing Havkin-Frenkel et al. (Food Technology, 1997, 51(11), 56-58, 61, Applicant's IDS) and Applicants' specification was not predicated on the idea that only overproducing a, or

the, rate-limiting step enzyme can be helpful in improving production of the end-product of a biosynthetic pathway. The line of reasoning set forth in the previous office action at pages 6-8 citing Havkin-Frenkel et al. (Food Technology, 1997, 51(11), 56-58, 61, Applicant's IDS) and Applicants' specification was predicated on the idea that it is unpredictable whether the overproduction of an enzyme associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde would improve the production of vanillin in *Vanilla planifolia*, as the chain shortening of p-coumaric acid to p-hydroxybenzaldehyde is but one of several steps required for vanillin biosynthesis (page 6 of the office action mailed May 6, 2004). The Examiner further maintains that the information disclosed in both the specification and the prior art regarding vanillin biosynthesis in culture and in planta underscore the unpredictability of the effect of overproducing an enzyme associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde, or any other vanillin biosynthetic enzyme, on vanillin production in *Vanilla planifolia*, since there is no clear indication whether or not the overproduction of an enzyme associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde having the amino acid sequence of SEQ ID NO:2 would improve the production of vanillin in *Vanilla planifolia*, or would cause a *Vanilla planifolia* cell or plant to produce at least twice as much vanillin as an equivalent plant that is not comparably genetically engineered.

The Examiner further maintains that in light of such unpredictability, it would require undue experimentation to practice the claimed invention, the ability of the skilled artisan to routinely measure vanillin not withstanding, as the undue experimentation required to practice the claimed invention lies not in the act of measuring vanillin, but in the act of optimizing, if possible, multiple variables in order to overproduce an enzyme associated with a chain

the, rate-limiting step enzyme can be helpful in improving production of the end-product of a biosynthetic pathway. The line of reasoning set forth in the previous office action at pages 6-8 citing Havkin-Frenkel et al. (Food Technology, 1997, 51(11), 56-58, 61, Applicant's IDS) and Applicants' specification was predicated on the idea that it is unpredictable whether the overproduction of an enzyme associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde would improve the production of vanillin in *Vanilla planifolia*, as the chain shortening of p-coumaric acid to p-hydroxybenzaldehyde is but one of several steps required for vanillin biosynthesis (page 6 of the office action mailed May 6, 2004). The Examiner further maintains that the information disclosed in both the specification and the prior art regarding vanillin biosynthesis in culture and in planta underscore the unpredictability of the effect of overproducing an enzyme associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde, or any other vanillin biosynthetic enzyme, on vanillin production in *Vanilla planifolia*, since there is no clear indication whether or not the overproduction of an enzyme associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde having the amino acid sequence of SEQ ID NO:2 would improve the production of vanillin in *Vanilla planifolia*, or would cause a *Vanilla planifolia* cell or plant to produce at least twice as much vanillin as an equivalent plant that is not comparably genetically engineered.

The Examiner further maintains that in light of such unpredictability, it would require undue experimentation to practice the claimed invention, the ability of the skilled artisan to routinely measure vanillin not withstanding, as the undue experimentation required to practice the claimed invention lies not in the act of measuring vanillin, but in the act of optimizing, if possible, multiple variables in order to overproduce an enzyme associated with a chain

shortening of p-coumaric acid to p-hydroxybenzaldehyde in a manner that would improve the production of vanillin in *Vanilla planifolia*, or in a manner that would produce a *Vanilla planifolia* cell or plant which produces at least twice as much vanillin as a non-genetically engineered cell.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 16, and claims 19-25 dependent thereon, is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 16 is indefinite in the recitation of "one or more enzymes associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde having the amino acid sequence of SEQ ID NO:2". It is unclear what object in the clause has the amino acid sequence of SEQ ID NO:2, "p-hydroxybenzaldehyde" or "one or more enzymes". If "one or more enzymes" has the amino acid sequence of SEQ ID NO:2, it is unclear which enzymes are encompassed by the claim, since the specification discloses only a single enzyme that has the amino acid sequence of SEQ ID NO:2 and that is associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (571) 272-0794. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Cynthia Collins
Examiner
Art Unit 1638

CC

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